Remarks

Favorable consideration of this application is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 1-12 and 14-20 are pending in the application. Claims 1-12 and 14-20 have been rejected. No new matter has been added.

Rejection Under 35 USC §112, Second Paragraph

Claims 1-12 and 14-20 are newly rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out the invention and distinctly claim the subject matter which applicant regards as the invention. The Examiner posits that step (a) of claim 1 is unclear because the "determination step" (i.e., "determining from a gene product of interest, a specific isoform of interest from said gene product") requires a plurality of gene products, and as a result "it is not clear how a single gene product may lead one to the various isoforms."

Applicants respectfully contend that there is confusion over the meaning of the "determination step," and hereby attempt to add some clarification. The addition of step (a) as part of the claim amendments in the response filed on April 10, 2007 and accompanying the RCE ("determining, from a gene product of interest, a specific isoform of interest from said gene product, and isoforms of said gene product not of interest") was made to address the outstanding claim rejections, which included §112, paragraph 1 rejections. By way of example, the addition of a "determination step" was made to refute the Examiner's repeated contention that the present claims lack enablement and written description because, e.g., a practitioner of the claims of the invention must possess knowledge of the plenary set of genes and gene products which are capable of being expressed by more than one isoform, or which have closely related sequences thereto. Applicants stand by their statement that a practitioner need only possess knowledge or her gene product of interest, which, although clear in the previous versions of claim 1, was made more explicit in the most recent amendments (i.e., the addition of the "determination step").

Applicants agree with the Examiner that "the determination [of an isoform of interest] can be made from all the products of a gene of interest." In fact, a practitioner most easily reaches a "specific isoform of interest" by knowing all the products of a gene of interest (i.e., by knowing all isoforms of all gene products of a gene of interest). An example of this is the oft-cited Example 1 of the present application, in which the Applicants isolate one ShcA isoform of the available three isoforms. It is the knowledge of all products of the ShcA gene of interest that easily enables the practitioner to isolate an isoform of interest (e.g., any one of p46ShcA, p66ShcA, or p52 ShcA) and knock down the other, non-desired isoforms.

According to this logic, the Examiner's statement that "[t]he determination [of an isoform of interest] can be made from all the products of a gene of interest" *supports* the Applicants' argumentation, and their addition of the "determination step." By the same token, Applicants feel the Examiner's statement that "[a]s said determination requires a plurality of gene products, it is not clear how a single gene product may lead one to the various isoforms" deserves special attention. Applicants feel the first part of that statement (i.e., before the comma), should read "[a]s said determination requires a plurality of *isoforms*," for there must be several known isoforms of a gene product of interest in order to determine an isoform of interest (and seek to knock-down the others). Regarding the second part of Examiner's statement (i.e., after the comma), Applicants respectfully admit to confusion. It is not the single gene product itself that leads to one of the various isoforms, but *knowledge* of the single gene product that leads to one of the isoforms (i.e., the isoform of interest).

So as to eliminate any potential confusion, the "determination step" presupposes of the practitioner (i) knowledge of a gene product of interest (e.g., the ShcA gene product, as encoded by the ShcA gene, in Example 1); and (ii) knowledge of an isoform of interest (e.g., the p66ShcA isoform, in the Examples). The determination is made possible by knowledge on the part of the practitioner.

Rejection Under 35 USC §112, First Paragraph- Written Description

Claims 1-12 and 14-20 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In addition to the arguments advanced in the prior Office Action responses (and while not acknowledging their insufficiency), and in addition to the explanation above, Applicants would like to reiterate their position in view of some of the Examiner's present statements.

Applicants feel the first part of the Examiner's statement on page 3, line 5 of the second paragraph to be in error ("Additionally arguing, that the products themselves (e.g., the encoded proteins) are not essential to the claimed methods of the invention…"). This is not the case. The products themselves *are* essential to the claimed methods, but it is *those precise gene products of interest* to the practitioner, versus *the plenary set of all gene products which are capable of being expressed by more than one isoform*. The latter is not essential, which is why the present claim set need not be commensurately broad with that plenary set (in terms of written description or enablement).

With regard to the last sentence of the first paragraph of page 4 of the Office Action ("The specification is further devoid of any description for a desired isoform replacing a mutant isoform or a tumor suppressive mutant isoform in a cell"), Applicants respectfully posit that there is nothing special about a mutant isoform or a tumor suppressive mutant isoform such that the

ShcA example given in the present specification would be an insufficient exemplification. In both the case of signaling adaptor/scaffold gene products and mutant/tumor suppressive mutant gene products, there can exist isoforms whose identities can be easily determined by a person of ordinary skill in the art. The knowledge of said isoforms that is a prerequisite of practicing the invention (especially with the addition of the "determining step") *is exactly the same*; therefore, the Examples of the present specification is sufficient, without additional need for an example concerning mutant/tumor suppressive mutant gene products and their isoforms.

The last two sentences of the next paragraph (first full paragraph on page 4 of the Office Action) read as follows: "Applicants have acknowledged that a skilled practitioner may utilize the instantly claimed method, when knowledge regarding the gene of interest, the isoforms and the sequences encoded thereby is already possessed. However, such knowledge is in fact absent from the instant specification, unless said practitioner wished to specifically express an isoform of the Shc gene." Applicants respectfully point out that "such knowledge is in fact absent from the instant specficiation" *because it constitutes the knowledge that a person of ordinary skill in the art already possesses prior to practicing the present invention.* In other words, if the practitioner already knows her gene of interest and isoform of interest (as well as the isoforms not of interest that she wishes to knock down), *then there is no need to learn the same from the present specification.*

Applicants respectfully hope that the Examiner's repeated rejections are reflective of a miscommunication on their part, which they have presently clarified, and thereby request removal of the same.

Rejection Under 35 USC §112, First Paragraph- Enablement

Claims 1-12 and 14-20 are rejected under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide an enablement for the full scope of the invention. Applicants first would like to thank the Examiner for removing certain aspects of the prior enablement rejections, and will concentrate on those remaining.

Contrary to the Examiner's assertions at the bottom of page 5 of the present Office Action, the present invention does not require "the complete suppression of expression of all isoforms, variants, mutants, etc." As seen throughout the present specification, isoforms not of interest are knocked down relative to those of interest, although not necessarily fully. For example, paragraphs **[0075], [0083],** and **[0086]** of the present published specification employ language to describe the expression of non-desired isoforms such as "low [expression]… [which] started to increase thereafter"; "almost completely"; and "very low." The important operating principle is that the expression level of the non-desired isoforms be lower relative to those levels of the desired isoforms, such that the latter can be easily detected despite the (minimal)

presence of the former. For this reason, the enablement standard is lower than described by the Examiner, and is met by the present specification for the present claims.

In an analogous fashion as described above, the shcA-related Examples of the present invention are sufficient to provide enablement for the scope of the present claims. There is nothing about the shcA gene product that would suggest it is easier or more difficult than other proteins in terms of the capacity of its isoforms to be selectively knocked down. The present methods of the invention apply to gene products of all types when in the hands of ordinarily skilled practitioners possessed with the knowledge of their isoforms of interest of their genes of interest.

With respect to the new enablement rejection, Applicants again turn to the "determination step" and the body of knowledge that it presupposes of the ordinarily skilled practitioner. As previously stated, the "determination step" presupposes of the practitioner (i) knowledge of a gene product of interest (e.g., the ShcA gene product, as encoded by the ShcA gene, in the present Examples); and (ii) knowledge of an isoform of interest (e.g., the p66ShcA isoform, in the Examples). One of the ways in which an isoform of interest (of a gene product of interest) become "of interest" to an ordinarily skilled practitioner is through a recognition that said isoform is capable of isolation, e.g., through the administration of RNAi. This can be easily determined scientifically, without undue experimentation.

As mentioned *supra*, the isoforms not of interest need only be knocked down *relative to those of interest, although not necessarily fully*. For this reason, the unpredictability of the field of RNAi is less of an issue, the enablement standard is lower than described by the Examiner, and the standard is thereby met by the present specification for the present claims

For the above-stated reasons, Applicants respectfully submit that the enablement rejections be removed.

Rejection Under 35 USC §101- Utility

The Examiner has raised a utility rejection for present claims 1-12 and 14-20, averring that there is no substantial utility- and therefore, no well established utility- present. Particularly, the Examiner contends that language in the present specification frames the present invention such that it "constitutes using the invention as an object of research in order to determine the function or effects of a specific isoform of interest, or to evaluate dsRNA inhibition, and does not meet the requirement for a substantial utility."

Applicants respectfully disagree. The present methods do not require further research in order to fully realize their utility; on the contrary, they possess a present utility, and enable further research in the field of molecular biology and therapeutic treatment of diseases, among others. In the same way that the present Examples show how signaling adaptor/scaffold gene

products such as ShcA can be studied in a substantial and meaningful way by the present invention, the present claims extend those findings to a wide variety of gene products. For at least these reasons, Applicants respectfully request removal of the present rejection.

Rejection Under 35 USC §102(e)

Claims 1-12 and 14-20 are rejected under 35 U.S.C. §102(e), as anticipated by Tuschl et al. (U.S. Patent Publn. No.: 2004/0259247)(hereafter, "the Tuschl reference"). Although the Tuschl reference and the claims of the present invention are similar in that both pertain to RNAi, Applicants respectfully disagree that the Tuschl reference anticipates the present claims. In fact, Applicants cite Tuschl publications related to the Tuschl patent application reference in the present application, as a way of describing past contributions to the RNAi field before distinguishing the present methods of the invention from any of the Tuschl work described. Applicants recognize that not every element of claims 1-12 and 14-20 is met by the Tuschl reference, and therefore respectfully request withdrawal of the §102(e) rejection.

The Tuschl reference lacks the all-important "determination step" that Applicants have cited throughout this response. As stated herein, this requires of the practitioner (i) knowledge of a gene product of interest (e.g., the ShcA gene product, as encoded by the ShcA gene, in Example 1); and (ii) knowledge of an isoform of interest (e.g., the p66ShcA isoform, in the Examples). As the purpose of the Tuschl methods is to knock down a gene of interest for therapeutic purposes, *irrespective of the presence of multiple isoforms*, said determination step is meaningless and not employed.

Applicants respectfully request entry of the amendments to the claims and the specification and submit no new matter is added thereby. Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

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